REMARKS

The Office Action dated October 12, 2007 has been received and carefully studied.

The Examiner sets forth the earlier restriction requirement made back in January of 2007, although the Examiner's recitation of that requirement is inaccurate, since Group III was not previously identified as such. Only groups I, II, IV and V were set forth in the January 2007 requirement. Nevertheless, the issue is moot, as the Examiner has withdrawn this restriction requirement in favor of a less restrictive requirement, wherein Group I is claims 1-14, drawn to cinnoline compounds, and a cell proliferation inhibitor comprising them, and Group I is claims 1-14, drawn to all other compounds of the formulae (1)-(4), and a cell proliferation inhibitor comprising them. Applicants hereby elect Group I.

The Examiner requests that the structural formulae be inserted into the Abstract. By the accompanying amendment, this change has been made.

The Examiner rejects claims 1, 2, 6, 13 and 14 under 35 U.S.C. §112, second paragraph, as being indefinite for various reasons. The Examiner states that the term

"analogue" is indefinite and confusing. By the accompanying amendment, this term has been deleted from the claims.

The Examiner states that in the definition of Y, the language "an amino acid residue which may be protected" is indefinite, because the terms "residue" and "protected" fail to particularly point out and distinctly claim the intended substituent groups. By the accompanying amendment, this phrase has been deleted from the claims.

Regarding a carbonyl group for B, by the accompanying amendment claim 2 has been amended to recite that the carbonyl group is formed together with A, thereby satisfying the valence.

Regarding the definition of W and W', the second recitation of "a phenyl group" is not inadvertent. The first "a phenyl group" is one of the substituents for "a lower alkyl group having 1 to 6 carbon atoms", and the second "a phenyl group" is one of the definitions for W and W'.

By the accompanying amendment, the spelling of "phenyl" has been corrected in claim 6.

The Examiner rejects claim 1 under 35 U.S.C. §102(b) as being anticipated by each of Nagarajan et al., Indian J. Chem., Vol. 25B, 1986, pp. 697-708, Altomare et al., J. Med. Chem., 1998, pp. 3812-3820, and Nagarajan et al., J. Med.

Chem., 1976, pp. 508-511; and claims 1 and 13 as being anticipated by each of Petrie et al., U.S. Patent No. 6,008,208 and Orme et al., U.S. patent No. 5,919,808.

By the accompanying amendment, claims 1-7, 9, 10 and 12 have been amended to recite a method of treating tumor in a subject. Claims 8, 11 and 13-14 have been cancelled. New claims have been added directed to a method for inhibiting cell proliferation by administering the recited compounds, as well as to the compounds themselves.

None of the cited references discloses or suggests the method for the treatment of tumor or the method of inhibiting cell proliferation, as now recited in the method claims. Accordingly, it is believed that the amendment overcomes the rejection.

With regard to the 3-phenyl-cinnoline compound as now claimed in claim 15, neither Nagarajan et al. (Indian J. Chem. Vol. 25B, 1986, pp. 697-708) nor Altomare et al. (J. Med. Chem., 1998, pp. 3812-3820) describes or suggests the claimed compounds which are cinnoline compounds wherein a substituted phenyl group is substituted at the 3-position of the cinnoline ring.

Also, Nagarajan et al. (J. Med. Chem., 1976, pp. 508-511) does not describe or suggest such claimed compounds.

Both Petrie et al. '208 and Petrie et al. '808 (referred to as Orme et al. by the Examiner) describe the treatment of bone deficits, and provide no disclosure of the methods as claimed in the amended claims of the present application. Therefore, it is believed that the methods as claimed in the amended claims are patentable over both Petrie et al. references.

With regard to the compounds as claimed in new claim 15, Petrie et al. '208 describes at FIG. 3A and FIG. 3B cinnoline compounds wherein two methyl groups are substituted at the 7-position of the cinnoline ring.

Petrie et al. '808 describes, as the third compound in both FIG. 4B and FIG. 4C, also cinnoline compounds wherein two methyl groups are substituted at the 7-position of the cinnoline ring.

To the contrary, the cinnoline compounds as claimed in new claim 15 have only one methyl group at the 7-position of the cinnoline ring. Therefore, the claimed compounds are very different from those described in both Petrie et al. references. Furthermore, neither Petrie et al. reference describes or suggests the inhibition activity on tumor or cell proliferation as exhibited by the cinnoline compounds of the present invention.

Furthermore, none of the Petrie et al. references describes or suggests the inhibition activity on tumor or cell proliferation as exhibited by the cinnoline compounds of the present invention.

Accordingly, it is believed that the claimed invention is novel and nonobvious over the cited references.

Reconsideration and allowance is respectfully requested in view of the foregoing.

Respectfully submitted,

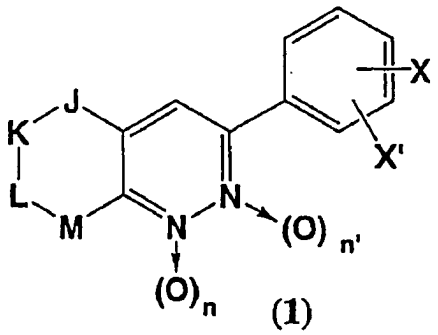
Kevin S. Lemack
Reg. No. 32,579
176 E. Main Street - Suite 5
Westboro, Massachusetts 01581
Tel: (508) 898-1818

Amendment to the claims

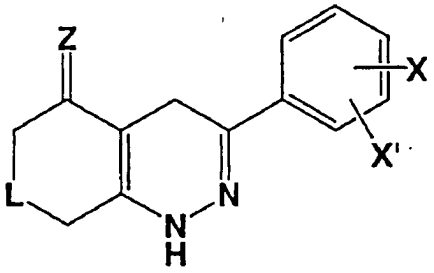
This listing of claims replaces all prior versions, and listings, of claims in the application.

Listing of Claims

1. (Currently amended) ~~An antitumor agent comprising~~ A method for the treatment of tumor in a subject, which comprises administering to said subject a 3-phenyl-cinnoline ~~analogue~~ compound represented by the following general formula (1) or (2):



(1)

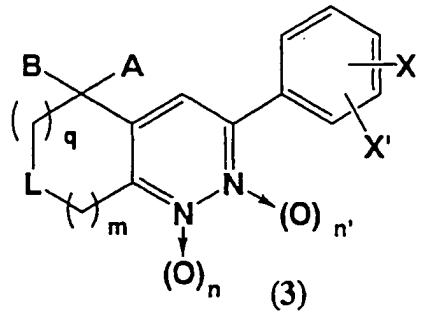


(2)

wherein J is A-C-B (C is a carbon atom); A is an O-Y group (O is an oxygen atom; Y is a hydrogen atom, a lower alkyl group having 1 to 6 carbon atoms which may be substituted by a phenyl group~~,~~ or a lower acyl group having 1 to 6 carbon atoms ~~or an amino acid residue which may be protected~~); B is a hydrogen atom, a lower alkyl group having 1 to 6 carbon atoms, or a carbonyl group together with A or $=N-NH_2$ ~~a substituted imino group~~ together with A; K is $(CH_2)_q$; L is ~~N-W (N is a nitrogen atom) or~~ W-C-W' (C is a carbon atom); W and W' each independently is a lower

alkyl group having 1 to 6 carbon atoms which may have a substituent selected from a group consisting of a hydroxyl group, a lower alkoxyl group having 1 to 6 carbon atoms and a phenyl group, a phenyl group, a carboxyl group, a lower alkoxycarbonyl group having 2 to 7 carbon atoms or a hydrogen atom; M is $(CH_2)_m$, or J-K-L-M is C(O-Y)=CH-C(W)=CH (Y and W have the same meanings hereinabove); Z is an oxygen atom ~~or N-Q (Q is an amino group, a lower alkylamino group, a hydroxyl group or a lower alkoxyl group)~~; X ~~and X' each independently~~ is a ~~lower alkyl group, a lower alkoxycarbonyl group, a lower acylamino group, a~~ lower alkoxyl group having 1 to 6 carbon atoms, a halogenated lower alkyl group having 1 to 6 carbon atoms, a nitro group, a cyano group~~,~~ or a halogen atom ~~or a hydrogen atom~~; X' is a halogen atom or a hydrogen atom; m and q ~~each independently is~~ are an integer of ~~0 to 3~~ 1; and n and n' each independently is 0 or 1, or a physiologically acceptable salt thereof ~~as an active ingredient~~.

2. (Currently amended) The ~~antitumor agent~~ method according to claim 1 wherein the 3-phenyl-cinnoline ~~analogue~~ compound is a compound represented by the following general formula (3):



(3)

wherein A is O-Y group (Y is a hydrogen atom, a lower alkyl group having 1 to 6 carbon atoms ~~which may be substituted by a phenyl group, a lower acyl group or an amino acid residue which may be protected~~); B is a hydrogen atom, a lower alkyl group having 1 to 6 carbon atoms, or a carbonyl group ~~or a substituted imino group~~ together with A; L is ~~N-W or~~ W-C-W'; W is a hydrogen atom and W' ~~each independently~~ is a lower alkyl group having 1 to 6 carbon atoms, ~~which may have a substituent selected from a group consisting of a hydroxyl group, a lower alkoxyl group and a phenyl group,~~ a phenyl group, a carboxyl group, a lower alkoxycarbonyl group having 2 to 7 carbon atoms or a hydrogen atom; X is a ~~lower alkyl group, a lower alkoxycarbonyl group, a lower acylamino group, a lower alkoxyl group, a~~ trifluoromethyl group, a nitro group, a cyano group or a halogen atom; X' is a ~~lower alkyl group, a lower alkoxycarbonyl group, a lower acylamino group, a lower alkoxyl group, a trifluoromethyl group, a nitro group, a cyano group, a halogen atom or a~~ hydrogen atom; m and q ~~each independently~~ is an integer of ~~0 to 3~~ 1; and n and n' each independently is 0 or 1.

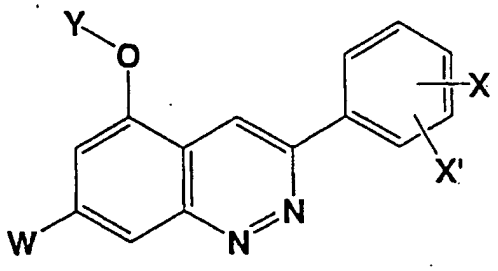
3. (Currently amended) The ~~antitumor agent~~ method according to claim 2, wherein B is a hydrogen atom; ~~L is W-C-W'; W and~~ W' ~~each independently~~ is a lower alkyl group having 1 to 6 carbon atoms ~~which may have a substituent selected from a group consisting of a hydroxyl group, a lower alkoxyl group and a phenyl group,~~ or a hydrogen atom;

X is a 3-trifluoromethyl group, a 3-nitro group, a 3-cyano group or a 3-bromo group; ~~X' is a hydrogen atom; m and q each individually is 1;~~ n is 0 or 1; and n' is 0.

4. (Currently amended) The ~~antitumor agent~~ method according to claim 3, wherein ~~W and W' each independently is a hydrogen atom or a lower alkyl group, and~~ X is a 3-trifluoromethyl group.

5. (Currently amended) The ~~antitumor agent~~ method according to claim 2, wherein ~~Y is a glycyl group, an alanyl group, a valyl group or an α-glutamyl group; B is a hydrogen atom;~~ L is H-C-CH_3~~; X is a 3-trifluoromethyl group; X' is a hydrogen atom; m and q each individually is 1; n is 0 or 1; and n' is 0~~.

6. (Currently amended) The ~~antitumor agent~~ method according to claim 1, wherein the ~~3-phneyl-cinnoline analogue~~ 3-phenyl-cinnoline compound is a compound represented by the following general formula (4):



(4)

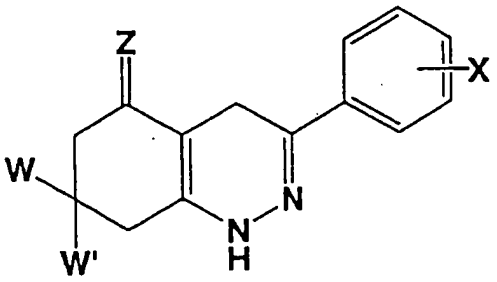
wherein X is a halogenated alkyl group having 1 to 6 carbon atoms; ~~and~~ X' ~~each independently~~ is a ~~lower alkyl group, a lower alkoxycarbonyl group, a lower acylamino group, a lower alkoxyl group, a trifluoromethyl group, a nitro~~

~~group, a cyano group, a halogen atom or~~ a hydrogen atom; Y is a lower alkyl group having 1 to 6 carbon atoms which may be substituted by a phenyl group, a lower acyl group having 1 to 6 carbon atoms or a hydrogen atom; and W is a lower alkyl group having 1 to 6 carbon atoms ~~which may have a substituent selected from a group consisting of a hydroxyl group, a lower alkoxyl group and a phenyl group, a phenyl group, a carboxyl group, a lower alkoxycarbonyl group or a hydrogen atom~~.

7. (Currently amended) The ~~antitumor agent~~ method according to claim 6, wherein X is a trifluoromethyl group~~, a nitro group, a cyano group or a halogen atom; X' is a hydrogen atom; and W is a lower alkyl group which may have a substituent selected from a group consisting of a hydroxyl group, a lower alkoxyl group and a phenyl group~~.

8. (Cancelled)

9. (Currently amended) The ~~antitumor agent~~ method according to claim 1 wherein a 3-phenyl-cinnoline ~~analogue~~ compound is a compound represented by the following general formula (5):



(5)

wherein W is a hydrogen atom; ~~and~~ W' ~~each independently~~ is

~~a hydrogen atom or~~ a lower alkyl group having 1 to 6 carbon atoms; X is a halogenated lower alkyl group having 1 to 6 carbon atoms; Z is an oxygen atom ~~or N-Q; Q is an amino group, a lower alkylamino group, a hydroxyl group or a lower alkoxyl group~~.

10. (Currently amended) The ~~antitumor agent~~ method according to claim 9, wherein ~~W is a hydrogen atom or a methyl group;~~ W' is ~~a hydrogen atom or~~ a methyl group; X is a 3-trifluoromethyl group~~; and Z is an oxygen atom~~.

11. (Cancelled)

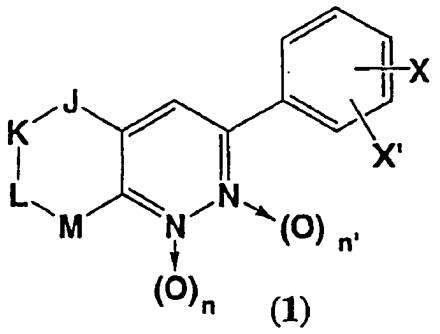
12. (Currently amended) The ~~antitumor agent~~ method according to claim 1 wherein the 3-phenylcinnoline ~~analogue~~ compound is 7-methyl-3-(3-trifluoromethylphenyl)-7,8-dihydro-6H-cinnolin-5-one, 7-methyl-3-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydrocinnolin-5-ol, 7-methyl-3-(3-trifluoromethylphenyl)cinnolin-5-ol, or 7-methyl-1-oxy-3-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydrocinnolin-5-ol~~, 5-glycyloxy-7-methyl-3-(3-trifluoromethyl)-5,6,7,8-tetrahydrocinnoline, 5-(L-alanyl)oxy-7-methyl-3-(3-trifluoromethyl)-5,6,7,8-tetrahydrocinnoline, 5-(L-valyl)oxy-7-methyl-3-(3-trifluoromethyl)-5,6,7,8-tetrahydrocinnoline, 5-(L-α-glutamyl)oxy-7-methyl-3-(3-trifluoromethyl)-5,6,7,8-tetrahydrocinnoline~~.

13. (Cancelled)

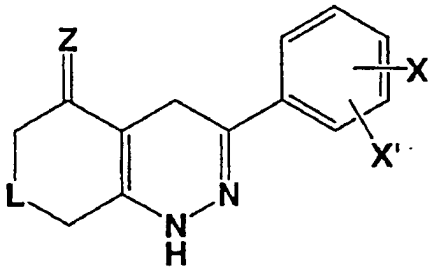
14. (Cancelled)

15. (New) A 3-phenyl-cinnoline compound represented

by the general formula (1) or (2):



(1)

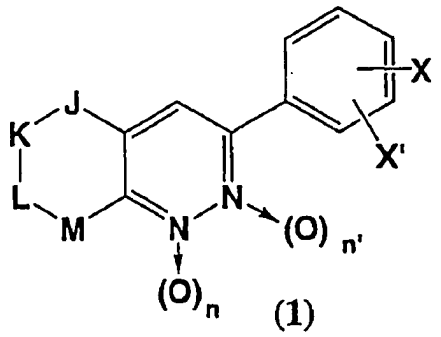


(2)

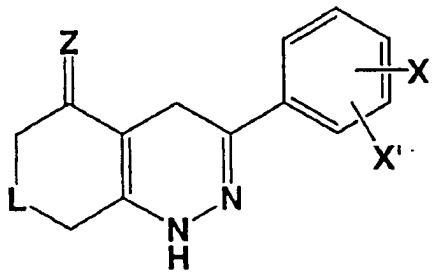
wherein J is A-C-B (C is a carbon atom); A is an O-Y group (O is an oxygen atom; Y is a hydrogen atom, a lower alkyl group having 1 to 6 carbon atoms which may be substituted by a phenyl group or a lower acyl group having 1 to 6 carbon atoms); B is a hydrogen atom, a lower alkyl group having 1 to 6 carbon atoms, or a carbonyl group together with A or $=N-NH_2$ together with A; K is $(CH_2)_q$; L is W-C-W' (C is a carbon atom); W is a lower alkyl group having 1 to 6 carbon atoms which may have a substituent selected from a group consisting of a hydroxyl group, a lower alkoxyl group having 1 to 6 carbon atoms and a phenyl group, a phenyl group, a carboxyl group, a lower alkoxycarbonyl group having 2 to 7 carbon atoms or a hydrogen atom; W' is a hydrogen atom; M is $(CH_2)_m$, or J-K-L-M is C(O-Y)=CH-C(W)=CH (Y and W have the same meanings hereinabove); Z is an oxygen atom; X is a lower alkoxyl group having 1 to 6 carbon atoms, a halogenated lower alkyl group having 1 to 6 carbon atoms, a nitro group, a cyano group, or a halogen

atom; X′ is a halogen atom or a hydrogen atom; m and q are an integer of 1; and n and n′ each independently is 0 or 1, or a physiologically acceptable salt thereof.

16. (New) A method for inhibiting cell proliferation, which comprises administering to a subject a 3-phenyl-cinnoline compound represented by the following general formula (1) or (2):



(1)

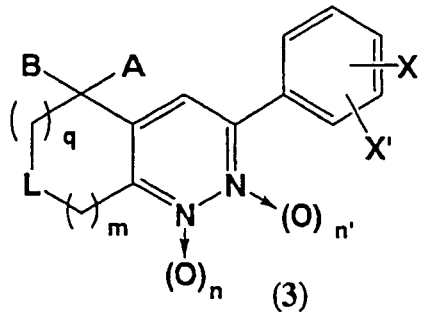


(2)

wherein J is A-C-B (C is a carbon atom); A is an O-Y group (O is an oxygen atom; Y is a hydrogen atom, a lower alkyl group having 1 to 6 carbon atoms which may be substituted by a phenyl group or a lower acyl group having 1 to 6 carbon atoms); B is a hydrogen atom, a lower alkyl group having 1 to 6 carbon atoms, or a carbonyl group together with A or $=N-NH_2$ together with A; K is $(CH_2)_q$; L is W-C-W′ (C is a carbon atom); W and W′ each independently is a lower alkyl group having 1 to 6 carbon atoms which may have a substituent selected from a group consisting of a hydroxyl group, a lower alkoxyl group having 1 to 6 carbon

atoms and a phenyl group, a phenyl group, a carboxyl group, a lower alkoxycarbonyl group having 2 to 7 carbon atoms or a hydrogen atom; M is $(CH_2)_m$, or J-K-L-M is C(O-Y)=CH-C(W)=CH (Y and W have the same meanings hereinabove); Z is an oxygen atom; X is a lower alkoxyl group having 1 to 6 carbon atoms, a halogenated lower alkyl group having 1 to 6 carbon atoms, a nitro group, a cyano group or a halogen atom; X' is a halogen atom or a hydrogen atom; m and q are an integer of 1; and n and n' each independently is 0 or 1, or the physiologically acceptable salt thereof.

17. (New) The method of claim 16, wherein said 3-phenyl-cinnoline compound is a compound represented by the following general formula (3):



(3)

wherein A is O-Y group (Y is a hydrogen atom, a lower alkyl group having 1 to 6 carbon atoms); B is a hydrogen atom, a lower alkyl group having 1 to 6 carbon atoms, or a carbonyl group together with A; L is W-C-W'; W is a hydrogen atom and W' is a lower alkyl group having 1 to 6 carbon atoms, a phenyl group, a carboxyl group, a lower alkoxycarbonyl group having 2 to 7 carbon atoms or a hydrogen atom; X is a trifluoromethyl group, a nitro group, a cyano group or a

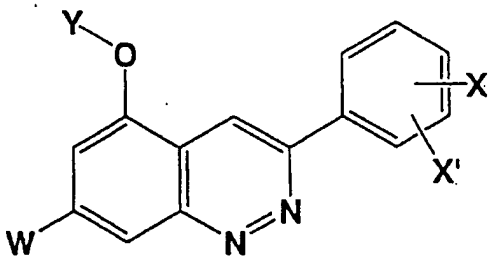
halogen atom; X' is a hydrogen atom; m and q is an integer of 1; and n and n' each independently is 0 or 1.

18. (New) The method according to claim 17, wherein B is a hydrogen atom; W' is a lower alkyl group having 1 to 6 carbon atoms or a hydrogen atom; X is a 3-trifluoromethyl group, a 3-nitro group, a 3-cyano group or a 3-bromo group; n is 0 or 1; and n' is 0.

19. (New) The method according to claim 18, wherein X is a 3-trifluoromethyl group.

20. (New) The method according to claim 17, wherein L is $H\text{-}C\text{-}CH_3$.

21. (New) The method according to claim 16, wherein the 3-phenyl-cinnoline compound is a compound represented by the following general formula (4):



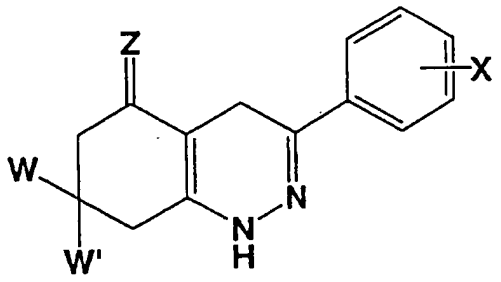
(4)

wherein X is a halogenated alkyl group having 1 to 6 carbon atoms; X' is a hydrogen atom; Y is a lower alkyl group having 1 to 6 carbon atoms which may be substituted by a phenyl group, a lower acyl group having 1 to 6 carbon atoms or a hydrogen atom; and W is a lower alkyl group having 1 to 6 carbon atoms.

22. (New) The method according to claim 21, wherein X

is a trifluoromethyl group.

23. (New) The method according to claim 16 wherein the 3-phenyl-cinnoline compound is a compound represented by the following general formula (5):



(5)

wherein W is a hydrogen atom; W' is a lower alkyl group having 1 to 6 carbon atoms; X is a halogenated lower alkyl group having 1 to 6 carbon atoms; Z is an oxygen atom.

24. (New) The method according to claim 23, wherein W' is a methyl group; X is a 3-trifluoromethyl group.

25. (New) The method according to claim 16 wherein the 3-phenylcinnoline compound is 7-methyl-3-(3-trifluoromethylphenyl)-7,8-dihydro-6H-cinnolin-5-one, 7-methyl-3-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydrocinnolin-5-ol, 7-methyl-3-(3-trifluoromethylphenyl)cinnolin-5-ol, or 7-methyl-1-oxy-3-(3-trifluoromethyl)-5,6,7,8-tetrahydrocinnolin-5-ol.